Formal Total Synthesis of Testudinariol A, a Triterpene with C_2 Symmetry

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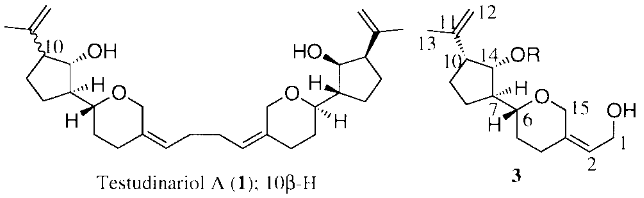
The alcohol corresponding to half of the molecule of testudinariol A, a triterpene with a symmetric C_2 structure isolated from *Pleurobrancus testudinarius*, was enantioselectively synthesized. The alcohol has been converted to testudinariol A by Mori et al.

Testudinariol A (**1**) is a triterpene ether isolated from the skin and mucus of *Pleurobrancus testudinarius*, together with its diastereomer, testudinariol B (**2**).[1] A characteristic feature of **1** is its symmetric C_2 structure and partially cyclized squalene skeleton.[2] The biologic role of **1** in mollusks is not known, but the substance is considered to act as a defensive allomone because it is ichthyotoxic against *Gambusia affinis*. As a part of synthetic studies of natural products using baker's yeast reduction of α-hydroxyketone,[3] an excellent method for chirality induction in terpenoid synthesis, we attempted enantioselective total synthesis of testudinariol A (**1**). Because **1** has a symmetric C_2 structure, dimerization of half of the molecule was the most effective strategy towards synthesizing **1**. Thus, a compound such as **3** is a potential synthetic intermediate in the present synthesis. Recent publication of the total synthesis of **1** by Mori and coworkers[4] prompted us to report our efforts to synthesize testudinariol A.[5] Herein, we report synthesis of the alcohol **3** (R = TBS), which was successfully converted to the natural testudinariol A by Mori's group.

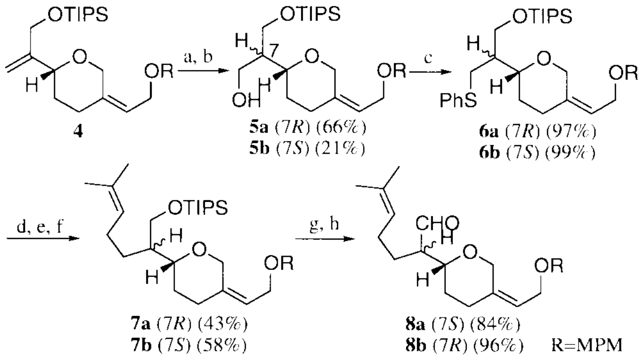


Testudinariol A (**1**): 10β-H
Testudinariol B (**2**): 10α-H
3

Figure 1. Structures of testudinariol A, B and the key intermediate.

In the course of our total synthesis of hippospongic acid A,[3,6] a triterpene possessing inhibitory activity for gastrulation of starfish embryos, we synthesized the dihydropyran derivative **4** in an optically pure form by the baker's yeast reduction of α-hydroxyketone derived from myrcene. This compound is a good precursor for the synthesis of **3** because introduction of a prenyl unit and subsequent cyclopentane ring formation provide the desired key intermediate **3**.

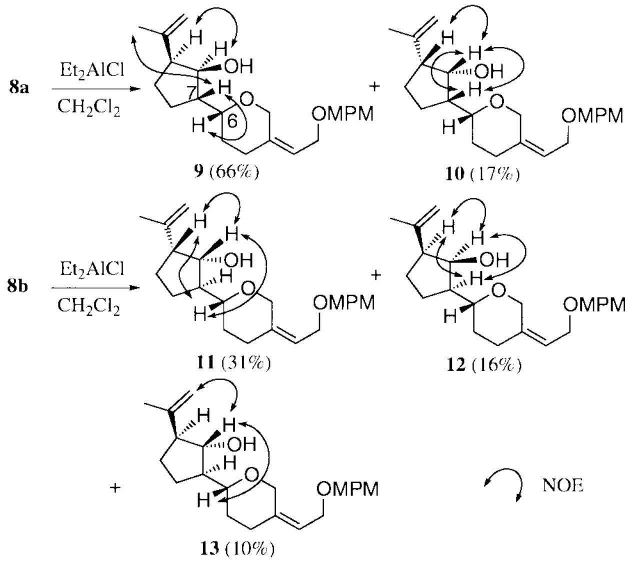
Hydroboration of **4** using 9-BBN afforded the epimeric alcohols **5a** and **5b** in ca. 3:1 ratio. As described below, the major product **5a** was suggested to have a (7*R*)-configuration. Because the stereochemistry at C7 could not be determined at this stage, we proceeded with the synthesis of the key intermediate **3**. The alcohol **5a** was sulfenylated using Hata's method[7] to give the thioether **6a**. Oxidation of **6a** with oxone,[8] prenylation of the resulting sulfone, followed by desulfonylation, yielded the prenylated product **7a**. Silyl ether was then removed and the resulting alcohol was oxidized to aldehyde **8a**. The minor product **5b** was also transformed into the aldehyde **8b** using the same sequence of reactions (Scheme 1).



Reagents: a. 9-BBN, THF; b. 30% H_2O_2, NaOH; c. PhSSPh, n-Bu_3P; d. Oxone, H_2O; e. $Me_2C{=}CHCH_2Cl$, n-BuLi, HMPA; f. Na(Hg), $Na_2HPO_4 \cdot 12H_2O$; g. n-Bu_4NF, THF; h. Swern oxidation.

Scheme 1.

The ene reaction[9] of **8a** using diethylaluminum chloride afforded two cyclopentanol derivatives **9** and **10**, while under the same conditions, **8b** gave three products **11**, **12**, and **13** (Scheme 2). The relative stereochemistries around the cyclopentane ring in each product were deduced on the basis of careful analyses of their NOESY spectra. At this stage, however, it was still difficult to determine the stereochemical relationship at C6 and C7. Comparison of the ^1H and ^{13}C NMR spectra

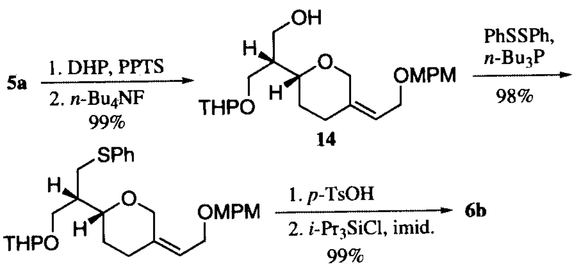


Scheme 2.

Table 1. ^{1}H and ^{13}C NMR chemical shifts of ene reaction products

	Posit.	1	9	10	11	12	13
^{1}H	5	1.41	1.50	1.53	1.41	1.45	1.44
		1.76	1.77	1.90	1.80	1.81	1.78
	6	3.18	3.49	3.71	3.21	3.58	3.38
	7	1.95	2.02	1.92	1.95	1.93	1.83
	8	1.22	1.51	1.25	1.21	1.22	1.23
		1.85	1.83	1.83	1.88	1.61	1.51
	9	1.67	1.67	1.73	1.69	1.76	1.85
		1.80	1.77	1.90	1.80	1.76	1.87
	10	2.40	2.83	2.42	2.39	2.35	2.48
	12	1.84	1.82	1.83	1.83	1.83	1.75
	13	4.82	4.84	4.84	4.82	4.83	4.80
		4.97	5.00	4.99	4.98	4.99	4.87
	14	4.18	4.02	4.16	4.17	4.28	3.84
	15	3.73	3.77	3.82	3.78	3.83	3.83
		4.59	4.56	4.56	4.59	4.58	4.58
^{13}C	5	32.0	31.4	32.4	31.8	32.9	32.6
	6	80.7	79.4	79.2	80.5	78.0	80.1
	7	53.1	52.6	52.9	53.0	52.4	53.2
	8	26.7	24.7	24.2	26.6	24.6	23.8
	9	27.2	27.0	24.9	27.1	24.7	26.7
	10	52.0	52.6	49.3	52.1	50.3	50.8
	11	144.4	144.0	144.1	144.3	144.3	145.9
	12	23.3	23.4	23.5	23.3	23.4	23.8
	13	112.1	112.6	111.8	112.3	111.5	110.4
	14	74.9	75.1	74.2	74.7	72.5	83.8
	15	66.7	66.6	66.4	66.5	66.4	66.4

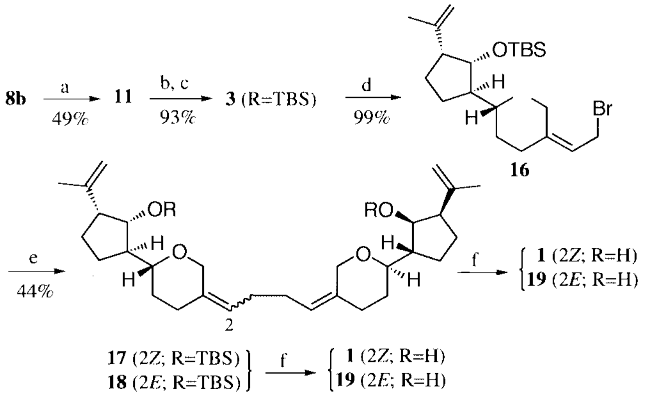
to those of natural **1** (Table 1) revealed that only **11** has the chemical shifts consistent with those of natural product [$\Delta\delta < 0.04$ ppm (^{1}H); $\Delta\delta < 0.2$ ppm (^{13}C)] suggesting that the isomer **11** was the desired compound, although the stereochemistry has not been established yet. Five of eight possible diastereomers were formed and the isopropenyl group and the hydroxy group in the products tend to have cis disposition. But clear explanation of the stereoselectivity of the ene reaction was difficult. To utilize the diastereomer formed in the hydroboration of **4**, **5a** was transformed into the thioether **6b** in 96% overall yield (Scheme 3).



Scheme 3.

It was necessary to improve the yield of **11** in the ene reaction of **5b**. In preliminary experiments using model compounds, we found that scandium triflate,[10] $Sc(OTf)_3$, is a better catalyst of the present ene reaction and we obtained the desired **11** in 49% yield together with 37% of the isomer mixture using 0.1 mol equivalent of $Sc(OTf)_3$. Thus, the obtained **11** was converted to the key synthetic intermediate **3** (R = TBS) by simple modification of the protective groups (Scheme 4).

Although successful synthesis of **3** (R = TBS) constitutes the formal synthesis of testudinariol A (**1**) because the alcohol thus obtained was identical to the compound prepared by Mori et al.,[3] we independently attempted the synthesis of **1** (Scheme



Reagents: a. $Sc(OTf)_3$, MS 4A; b. TBSOTf, 2,6-lutidine; c. DDQ, $NaHCO_3$; d. CBr_4, Ph_3P; e. $Ni(cod)_2$, DMF; f. n-Bu_4NF

Scheme 4

4). Thus, **3** (R = TBS) was converted to the bromide **16**, which was treated with $Ni(cod)_2$[11] to yield a mixture in moderate yield, whose NMR spectra obviously showed that the mixture consisted of **17** and **18** (ca. 1:1). But separation of these isomers was totally unsuccessful. The difficulty in separation was not improved by deprotecting to the alcohol mixture (**1** and **19**). The detailed comparison of the ^{1}H and ^{13}C NMR spectra[12] of the obtained mixture with those of natural testudinariol A clearly revealed the presence of testudinariol A (**1**) in the mixture.

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12 Selected NMR chemical shifts of **1**; ^{1}H NMR δ ($CDCl_3$) 1.84 (6H, s), 2.40 (2H, ddd, J = 5.8, 5.8, 11.6 Hz), 3.19 (2H, dd, J = 8.7, 8.7 Hz), 3.73 (2H, d, J = 12.9 Hz), 4.18 (2H, m), 4.59 (2H, d, J = 12.9 Hz), 4.82 (2H, s), 4.97 (2H, s), 5.17 (2H, t-like, J = 6.3 Hz); ^{13}C NMR δ ($CDCl_3$) 23.3, 26.7, 27.2, 27.3, 32.0, 33.0, 52.0, 53.1, 66.7, 74.8, 80.7, 112.2, 123.4, 134.3, 144.4.